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ORIGINAL ARTICLE

Enoxaparin and aspirin therapy for recurrent pregnancy loss due to anti-phospholipid syndrome (APS)

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KEYWORDS
Anticoagulation; Antiphospholipid syndrome; Enoxaparin; Aspirin; Pregnancy; Recurrent miscarriage

Abstract  Background: Recurrent miscarriage affects 1–2% of women. Thrombophilia included antiphospholipid syndrome has been identified in about 50% of women with recurrent miscarriage. Aspirin and heparin therapy is frequently prescribed for APS, yet there is no robust evidence for the most efficacious regime.

Objective: To determine maternal and foetal outcomes in women with APS managed with aspirin or enoxaparin plus aspirin during pregnancy.

Design: Prospective non randomized study.

Setting: High-risk pregnancy unit-Benha University Hospital.

Methods: Seventy selected patients during pregnancy with clinical and/or serological findings of antiphospholipid syndrome were divided into two Groups: Group A (n = 47) had received aspirin (81 mg once daily orally) plus LMWH enoxaparin (40 mg subcutaneously/day) while Group B (n = 23) had received low-dose aspirin (81 mg day orally).

Main outcome measures: Maternal outcomes included thromboembolic, haemorrhagic complications and pregnancy-induced hypertension. Prematurity, intrauterine growth restriction and neonatal death were considered as foetal complications.

Results: There were significant differences between Groups A and B in the rate of miscarriages (4 in Group A (9%) versus 8 in Group B (35%); p = 0.02), number of live births (43/47(91%) versus 15/23(65%); p = 0.02), mean gestational age (37.86 ± 1.8 versus 36.13 ± 2.39 weeks; p = 0.005), neonatal birth weight (3252 ± 459 versus 2907 ± 618 g; p = 0.03) and rate of pre-eclampsia (3/43 (7%) versus 6/15 (40%); p = 0.009). Although not statistically significant, women in Group
1. Introduction

Nowadays, APS is recognized as the most significant cause of RPL (recurrent pregnancy loss). In women with RPL, the incidence of APS is between 20% and 40%. Some authorities claim that the unifying feature of these processes is abnormal placental function due to necrosis, infarction and thrombosis. Some others associate abnormalities in the decidual spiral arteries with foetal loss in APS especially thickening, atherosclerosis and fibrinoid necrosis. These conditions may result from thrombosis during the development of the normal maternoplacental circulation. However, there is a wide variety of related clinical manifestations, and obstetric morbidity is one of the major manifestations of APS. There are three primary classes of antibodies associated with the antiphospholipid syndrome: (1) anticardiolipin antibodies (aCL), (2) the lupus anticoagulant (LA) and (3) antibodies directed against specific molecules including a molecule known as beta-2-glycoprotein 1 (anti-b2GPI). Lupus antibody is the most powerful predictor of thrombosis and recurrent miscarriages. Anti-b2-glycoprotein-I antibodies are not associated with recurrent miscarriage in isolation; however, in combination with positive results for lupus anticoagulant (LA) and aCL, there is a high risk of obstetric complications.1

Antiphospholipid antibodies can be detected in 1–5% of healthy women. The prevalence of positive antiphospholipid antibodies increases to 15% in women with recurrent first trimester pregnancy losses and up to 20% in women suffering a stroke at or before the age of 50 years. Around 40% of women with lupus have antiphospholipid antibodies; it is estimated that less than 40% of them will eventually develop thrombotic events. The prevalence of APS is unknown, but it has been estimated to be 0.5% in the general population.2

Antiphospholipid antibodies bind to negatively charged phospholipids, protein-binding phospholipids, or both, triggering the activation of endothelial cells, monocytes and platelets. In addition, antiphospholipid antibody complexes, mainly formed by b2 glycoprotein I and anti-b2 glycoprotein I, activate the classical and alternative complement pathways. Therefore, complement deficiency or inhibition of complement activation proved to have a protective effect against pregnancy loss and thrombosis in a murine model. This fact could explain the benefits of low dose heparin, owing to its capacity of complement inactivation rather than by its antithrombotic effects.3

Our understanding of the aetiology and pathogenesis of the antiphospholipid syndrome is limited, but it has generally been considered a thrombophilic disease and hence treatment has focused on anticoagulation. Agents such as aspirin and heparin administered alone or in combination have been used in the management of obstetric patients with APS. Recent findings from research in animal models of APS challenge the dogma that this syndrome is a non-inflammatory, thrombotic disease and provide evidence that activation of complement is crucial for development of complications in pregnancy.4

A sporadic spontaneous abortion occurs in up to 15% of all recognized pregnancies, and recurrent miscarriage occurs in about 1% of women at reproductive age. They can be caused by chromosomal, anatomic, hormonal (progesterone, oestrogens, diabetes or thyroid disease), coagulation or platelet abnormalities. Taking into account all possible causes, APS could be responsible for 10–15% of recurrent miscarriages, whereas antiphospholipid antibodies could be identified in 5–20% of these women.5

Early onset, severe preeclampsia, complicated with HELLP syndrome (haemolysis, liver enzyme elevation and thrombocytopenia), is a frequent association probably due to shared pathogenic mechanisms. In the general obstetric population, the incidence of HELLP is between 0.01% and 0.2% while in pregnancies complicated by preeclampsia/eclampsia, an incidence of 10–12% has been reported. About one-third of untreated women with APS may develop pre-eclampsia during pregnancy, and more than 10% of these women will deliver small for gestational age infants.6

Several mechanisms have been proposed to explain the role of presence of antiphospholipid antibodies in the pathogenesis of hypercoagulable state of APS. Firstly these antibodies have been shown to cause endothelial cell and monocyte activation, leading to a prothrombotic phenotype, which is characterized by the expression of adhesion molecules and tissue factors. In order to activate these effector cells and cause thrombosis antiphospholipid antibody b2GPI complexes interact with cell surface receptors, such as annexin II receptors which induces a signalling cascade.8 Secondly, platelets also become prone to aggregate after exposure to antiphospholipid antibodies as β2GP1 dimers bound to antiphospholipid antibodies on platelets interact with the apolipoprotein E2 receptor to trigger the activation and release of thromboxane, which facilitates platelet aggregation; not only this, thrombosis in the placenta and other vascular beds is induced by antiphospholipid antibody mediated interference with the annexin A5 anticoagulant shield on phospholipid surfaces of trophoblasts and impairment of both intrinsic and extrinsic fibrinolysis.9

Furthermore, antiphospholipid antibodies have been shown to alter the maturation and invasiveness of trophoblast cells in vitro. This suggests that the antibodies cause defective placentation and that thrombophilia is not the sole...
explanation for complications of pregnancy in patients with APS. This theory is also supported by the observation that therapies for pregnant women with APS aimed at preventing thrombosis are only partly successful at averting pregnancy loss. \(^8\)

Clinical manifestations may range from no symptoms to immediately life threatening catastrophic APS \(^9\). Primary APS is defined as presence of aPL antibodies in patients with idiopathic thrombosis but no evidence of autoimmune disease. Secondary APS is used when patients with a wide spectrum of autoimmune disorders (primarily SLE and rheumatoid arthritis) and thrombosis are also found to have antiphospholipid antibodies \(^10\). Probable APS is one in which there are typical clinical manifestations but without positive serological test of aPL. These are also called seronegative APS or pre APS. \(^11\)

Without treatment the miscarriage rate in a subsequent pregnancy in this condition is as high as 90%. It is widely accepted that treatment with low dose aspirin and heparin or low molecular weight heparin (LMWH) significantly improve outcome as compared to previous untreated pregnancies. \(^12\)

Use of low dose of aspirin and low molecular weight heparin (Enoxaparin) is safe in pregnancy and it improves foetal outcome. \(^13\) Bleeding is a potential complication of anticoagulant therapy, heparin induced thrombocytopenia has been observed less commonly in patients treated with LMWH. LMWH do not cross the placenta and therefore are not associated with bleeding in foetuses and have few teratogenic effects. \(^14\) LMWH have higher specificity for Xa and have fewer effects on platelet activity. As a result LMWH may cause bleeding less often, while still retaining anticoagulant effects. The LMWH are associated with less risk of heparin induced osteoporosis.

A number of studies have evaluated the efficacy of treatment with low-dose aspirin, prednisolone, unfractionated low-molecular weight heparin and most recently intravenous gamma globulin, either alone or in various combinations. However, the findings have not been consistent. \(^15\) Low-dose aspirin in combination with heparin was demonstrated in two randomized controlled trials to lead to a significant improvement in the live birth rate. \(^16\) This study aimed to determine the pregnancy outcome in women with APS and recurrent pregnancy loss who were treated with aspirin alone or aspirin in combination with heparin during the index pregnancy.

2. Patients and methods

This prospective non randomized comparative study was conducted at the Department of Obstetrics and Gynecology, Benha University Hospital, and a private centre, since June 2012 till November 2013. After approval of the study protocol by the Local Ethics Committee a written fully informed patients’ consent was obtained. All patients were interviewed about their medical, personal, family, obstetrical and thrombosis history. All patients included in the study met the strict clinical criteria for diagnosis of Antiphospholipid syndrome which is as follows.

2.1. Clinical criteria

2.1.1. Vascular Thrombosis

One or more episodes of arterial, venous or small vessel thrombosis in any tissue or organ.

2.1.2. Pregnancy morbidity

(a) One or more unexplained deaths of morphologically normal foetuses at or after 10 weeks of gestation with normal foetal morphology documented by ultrasound or direct foetal examination.

(b) One or more premature births of morphologically normal foetuses before 34 weeks of gestation because of:

(i) Eclampsia or severe pre-eclampsia defined according to standard definitions or

(ii) Recognized feature of placental insufficiency.

(c) Three or more unexplained consecutive spontaneous abortions before10 weeks of gestation with maternal anatomic or hormonal abnormalities and parental chromosomal causes excluded.

2.2. Laboratory criteria

(1) Lupus anticoagulant (LA): In plasma, present on two or more occasions at least 6–12 weeks apart.

(2) Anti-cardiolipin (aCL) of IgG and/or IgM isotype: in serum or plasma present in medium or high titres at least 6–12 weeks apart.(Definite antiphospholipid syndrome may be diagnosed if at least one of the clinical criteria and at least one of the laboratory criteria are met)

All patients (n = 70) were offered baseline tests including aCL, LA and repeated after 12 weeks before pregnancy and findings noted. All selected patients were in good general health without previous history of Diabetes Mellitus or thyroid dysfunction or cardiac disease. Patients with thrombocytopenia (<100,000/ml), bleeding tendencies, ectopic pregnancy and multiple gestation were excluded from the study. Baseline complete blood picture, routine urine examination, blood sugar, blood Grouping, Bleeding Time, Clotting Time, Prothrombin Time and Activated Partial Thromboplastin Time. Hepatitis B Surface Ag and Hepatitis C Virus screening were offered to all patients and findings noted as soon as they conceived. Anti Xa level were not tested. All selected patients were given routine Folic Acid, Iron and Calcium supplementation orally daily during antenatal period (whether conceived spontaneously or with treatment).

All were put on tab aspirin 81 mg/day (Juspirin) daily as soon as gestational sac was visible on ultrasound at around 6 weeks. Then Group A (47 pregnant) were put on Inj. Enoxaparin (Clexane) 40 mg subcutaneous once a day when cardiac activity was seen on ultrasound (at around 7–8 weeks), Inj. Enoxaparin was given either into anterior abdominal wall or anterior aspect of thigh subcutaneously.

While Group B (23 pregnant) received aspirin 81 mg/day (Juspirin) daily, no woman experienced any major haemorrhagic event during pregnancy labour or post-partum. Three patients developed mild unexplained vaginal bleeding which settled by expectant management. Discontinuation of medicine was not required due to haemorrhagic problems. Patients were advised to visit fortnightly.

Foetal growth was monitored by fundal height measurement and serial ultrasounds. Doppler umbilical wave flow velocity was studied for foetuses with suspected intrauterine
growth retardation. All patients were given aspirin 81 mg daily till 35 completed weeks. Aspirin was stopped to allow Ductus Arteriosis closure and prevent bleeding in labour Inj. Enoxaparin was given till 37 weeks and stopped thereafter to reduce risk of epidural haematoma in case patient required anaesthesia for caesarean delivery. For some patients aspirin and enoxaparin were discontinued earlier due to abortion, preterm labour, intrauterine growth retardation or pre-eclampsia leading to premature delivery.

2.3. Outcome evaluation

The primary outcome measure was the rate of live births. Secondary outcomes included rates of miscarriage, intrauterine foetal death (foetal death after 20 weeks of gestation), and obstetrical complications. Such complications included pre-eclampsia, small size for gestational age (birth weight below the 10th percentile for gestational age and sex), placental abruption, and premature delivery.

2.4. Statistical analysis

Results were expressed as mean ± SD, range, numbers and percentages. Intra-Group data was statistically analysed using t-test and inter-Group analysis was examined using Chi-square test (X² test). Statistical analysis was conducted using SPSS statistical program, (Version 10, 2002). P value < 0.05 was considered statistically significant.

3. Results

A total of 70 women with APS were included in the study: 47 women in Group A used low-dose aspirin (jusprin) plus LMWH (clexane) and 23 women in Group B received low-dose aspirin only. Table 1 shows the demographic details of the women. There were no significant differences in the patient’s age at entry, weight, prior pregnancies, prior live births, prior miscarriages and prior IUFD.

As shown in Table 2, there was a highly significant difference between Groups A and B in the rate of miscarriages (4 miscarriage in Group A (9%) versus 8 miscarriages in Group B (35%); p = 0.02). Most miscarriages in the two Groups occurred in the first trimester (3 in Group A and 5 in Group B).

In the low-dose aspirin plus LMWH (Group A) there were a significantly greater number of live births (43/47(91%) versus 15/23(65%); p = 0.02).

The mean gestational age at the neonatal birth weight were significantly higher in Group A than in Group B. The mean gestational age at delivery in Group A was 37.86 ± 1.8 versus 36.13 ± 2.39 weeks in Group B; p = 0.005. The mean birth weight in Groups A was 3252 ± 459 versus 2907 ± 618 g in Group B; p = 0.03. There were no intrauterine or neonatal deaths in the study (Table 3).

The rates of pre-eclampsia was significantly higher in Group A than in Group B (3/43 (7%) versus 6/15 (40%); p = 0.009).

Although not statistically significant, women in Group A tended to have lower rates of preterm births (6/43 (14%) versus 3/15 (20%); p = 0.89) and IUGR (5/43 (12%) versus 5/15 (33%); p = 0.13) than in Group B (Table 4). Also there was no statistically significant difference in the mode of delivery.

Nineteen of the 58 women with successful pregnancies (33%) delivered prematurely (< 37 weeks’ gestation). Eleven of them were in Group A [6/43 (14%) due to preterm labour, 4/43(9%) due to IUGR, and 1/43(2%) due to pre-eclampsia] and the remaining 8 were in Group B [3/15(20%) due to preterm labour, 3/15(20%) due to IUGR and 2/15 (13%) due to pre-eclampsia]. No woman developed a thromboembolic complication during pregnancy or the puerperium (Table 3).

All babies were examined by a paediatrician shortly after delivery. No congenital abnormalities were detected.

Twelve babies were admitted to the neonatal unit because of prematurity. Nine babies (5 in Group A and 4 in Group B), delivered by caesarean section for IUGR and preeclampsia, required ventilator support for a week. The other three babies (1 in Group A and 2 in Group B) were admitted to the neonatal unit for help with feeding.

Both low dose aspirin and LMWH were well tolerated. Of those taking heparin, none developed thrombocytopenia or had symptomatic complications apart from mild bruising localized to the injection site.

4. Discussion

The negative effect of APS on pregnancy is most likely tied to abnormal placental function.19 Adverse pregnancy outcomes in women with APS may result from poor placental perfusion due to localized thrombosis, perhaps through interference by APA antibodies with trophoblastic annexin V.20

Activated endothelial cells express adhesion molecules and, along with monocytes, up regulate the production of tissue factor. Tissue factor is the major initiator of the coagulation cascade in vivo, playing an important role in thrombosis and inflammation. Growing evidence suggests that antiphospholipid antibodies-dependent induction of tissue-factor activity on circulating monocytes is an important mechanism of hypercoagulability in APS. Tissue factor, acting as a proinflammatory

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Age and pregnancy characteristics of women treated with aspirin plus LMWH or aspirin only.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>LMWH + aspirin Group A (n = 47)</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>28.7 ± 3.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.8 ± 7.62</td>
</tr>
<tr>
<td>Total pregnancies</td>
<td>3.98 ± 1.67</td>
</tr>
<tr>
<td>Prior abortions (No.)</td>
<td>2.98 ± 1.33</td>
</tr>
<tr>
<td>Prior live births (%)</td>
<td>26/47(55%)</td>
</tr>
<tr>
<td>prior IUFD (No.)</td>
<td>22/47(47%)</td>
</tr>
</tbody>
</table>

Data are presented as percentage or mean ± standard deviation.
molecule, enhances neutrophil activity causing trophoblastic injury, placental dysfunction and damage in the developing placenta and embryo. In addition, antiphospholipid antibodies seem to cause direct trophoblastic dysfunction, resulting in impaired transplacental exchange between the mother and the fetus, which can lead to early miscarriage, pre-eclampsia, intrauterine foetal growth restriction or even intrauterine foetal death. The disruption of the annexin A5 shield also plays an important role in the pathogenesis of APS. Annexin A5 is a potent vascular and placental anticoagulant protein, which has high affinity for negatively charged phospholipids. It is highly expressed on the apical membranes of placental villous syncytiotrophoblast, at the interface between the fetus and the placenta. Its anticoagulant effect results from the capacity to crystallize over phospholipid bilayers, blocking their availability for coagulation reactions. Antiphospholipid antibodies interfere with annexin A5 function, leading to accelerated coagulation reactions, and probably contributing to pregnancy loss and to the thrombogenic effects of these antibodies.

The optimal treatment of pregnant women with APS is combination therapy with low molecular weight heparin (5000 units subcutaneously daily) and aspirin 75–100 mg daily. The management of obstetric APS is still controversial. In discussing the literature we divided patients into two categories.

The therapeutic benefit of heparin is thought to arise from its ability to bind aPL. By doing so, the pathological interaction between aPL and the trophoblastic and maternal decidual vessels is inhibited, and placentation is more likely to be successful. Later in pregnancy the anticoagulant properties of heparin are likely to be beneficial in reducing the risk of placental thrombosis and infarction. Aspirin, by inhibiting platelet aggregation, also has a favourable thromboprophylactic effect. Unfractionated and low molecular weight heparins have been shown to be equally beneficial in the treatment of women with PAPS, the latter having the advantage of being a once daily injection. Women may also be reassured that the modest loss in BMD observed with heparin therapy is not significantly different from the natural physiological loss in BMD seen in normal pregnancy.

Some investigators have found narrowing of spiral arteries, intimal thickening, acute atherosclerosis and fibrinoid necrosis in the placenta of women with foetal loss associated with APS. Others have found extensive placental necrosis, infarctions and thrombosis. APAs may activate endothelial cells as indicated by tic effect. Unfractionated and low molecular weight heparins platelet aggregation, also has a favourable thromboprophylactic effect. Unfractionated and low molecular weight heparins

### Table 2 Outcome data from patients who had miscarriage.

<table>
<thead>
<tr>
<th>Variables</th>
<th>LMWH + aspirin Group A (n = 47)</th>
<th>Aspirin alone Group B (n = 23)</th>
<th>Test of significance</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriages (%)</td>
<td>4/47(9%)</td>
<td>8/23(35%)</td>
<td>$X^2 = 5.77$</td>
<td>0.02</td>
</tr>
<tr>
<td>EGA at loss</td>
<td>10.75 ± 4.99</td>
<td>12.38 ± 3.34</td>
<td>$T = 0.68$</td>
<td>0.51</td>
</tr>
</tbody>
</table>

### Table 3 Outcome data from patients who had live births.

<table>
<thead>
<tr>
<th>Variables</th>
<th>LMWH + aspirin Group A (n = 47)</th>
<th>Aspirin alone Group B (n = 23)</th>
<th>Test of significance</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births (%)</td>
<td>43/47(91%)</td>
<td>15/23(65%)</td>
<td>$X^2 = 5.77$</td>
<td>0.02</td>
</tr>
<tr>
<td>EGA at birth (weeks)</td>
<td>37.86 ± 1.8</td>
<td>36.13 ± 2.39</td>
<td>$T = -2.91$</td>
<td>0.005</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>3252 ± 459</td>
<td>2907 ± 618</td>
<td>$T = -2.28$</td>
<td>0.03</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>(n = 43)</td>
<td>(n = 15)</td>
<td>$X^2 = 0.01$</td>
<td>0.92</td>
</tr>
<tr>
<td>1. Caesarean Section</td>
<td>30(70%)</td>
<td>10(67%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Vaginal delivery</td>
<td>13(30%)</td>
<td>5(33%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4 Obstetric and maternal complications of patients who delivered a live born.

<table>
<thead>
<tr>
<th>Variables</th>
<th>LMWH + aspirin Group A (n = 43)</th>
<th>Aspirin alone Group B (n = 15)</th>
<th>Test of significance</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia (No.)</td>
<td>3(7%)</td>
<td>6(40%)</td>
<td>$X^2 = 6.89$</td>
<td>0.009</td>
</tr>
<tr>
<td>Preterm delivery (No.)</td>
<td>6(14%)</td>
<td>3(20%)</td>
<td>$X^2 = 0.02$</td>
<td>0.89</td>
</tr>
<tr>
<td>IUGR (No.)</td>
<td>5(12%)</td>
<td>5(33%)</td>
<td>$X^2 = 2.3$</td>
<td>0.13</td>
</tr>
<tr>
<td>Prematurity (No.)</td>
<td>11(26%)</td>
<td>8(53%)</td>
<td>$X^2 = 2.73$</td>
<td>0.1</td>
</tr>
</tbody>
</table>

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Group B (40%); \((P < 0.009)\). These results are comparable to international data. A prospective study by Kutteh revealed that viable infants were delivered 20/25 (80%) women treated with heparin and aspirin and of 11/25 (44%) women treated with aspirin \((p < 0.05)\) and this agreed with our present study \((43/47(91\%)\) versus 15/23(65\%); \(p = 0.02\)). But there were no significant differences between the low-dose aspirin and the heparin plus low-dose aspirin Groups with respect to gestational age at delivery \((37.2 \pm 3.4\) weeks vs. \(37.8 \pm 2.1\) weeks) these disagreed with our results \((37.86 \pm 1.8\) versus 36.13 \(\pm 2.39\) weeks; \(p = 0.005\)), while agreed with ours in difference in number of caesarean sections, or complications. A comparable trial also found aspirin alone inferior to aspirin plus heparin \(42\%\) versus 71\% live births\). But, Farquharson et al., found the birth rate to be similar in both Groups \(72\%\) with aspirin alone compared with 78\% when heparin was added to the regimen. 

In a randomized prospective study done by Fouda et al., found that LMWH plus aspirin was successfully used as an alternative to UFH plus aspirin in the management of recurrent abortion secondary to APS. \(80\%\) in the LMWH Group and Group \(66.67\%\) in the UFH, delivered a viable infant \((P = 0.243)\) these results were comparable to our results. Backos et al., agreed with our present study in that combination treatment with aspirin and heparin leads to a high live birth rate among women with recurrent miscarriage and antiphospholipid antibodies \(71\%\) resulted in a live birth and \(27\%\) miscarried, the majority in the first trimester. 

Our study suggests that the women with APS and in pregnancy can be treated effectively with low-dose aspirin alone. As this study did not include untreated controls, we cannot exclude the possibility that aspects of obstetric care other than the treatment influenced pregnancy outcome. There have been a number of randomized control trials for patients with APS evaluating either unfractionated heparin (UFH) or LMWH over the past 15 years. Each trial determined its inclusion criteria the live birth rates were similar ranging from 71.1\% to 84\%. The only significant differences among trial outcomes were in the low-dose aspirin only treatment arms: the live birth rates in those varied from a low of 42.2\% to a high of 80\%. \(17,23\)

To date, studies confirmed that treatment with LMWH plus aspirin should be considered as the standard therapy for recurrent pregnancy loss due to APS. \(28,29\)

The main limitation of this study that it was non randomized study which can be explained by the need of active participation of the patients in buying the medication (cost implication).

5. Conclusion

Combination treatment with aspirin and LMWH leads to a high live birth rate among women with recurrent miscarriage and antiphospholipid antibodies. This combination may promote successful embryonic implantation in the early stages of pregnancy and protect against thrombosis of the uteroplacental vasculature after successful placentation. Future studies should be aimed at refining the protocol used in this trial to determine the benefits of preconceptional administration of heparin and whether it can be stopped after 13 weeks’ gestation without adversely affecting the rate of live births.

However, successful pregnancies are prone to a high risk of complications during all trimesters. Close antenatal surveillance and planned delivery of these pregnancies in a unit with specialist obstetric and neonatal intensive care facilities are indicated.

Solid conclusions from this study are limited due to small number of patients, non-randomization of groups and discrepancy in number between groups and that a larger RCT is needed.

6. Recommendation

A larger RCT is needed.

Conflict of interest

The authors declare that they have no conflict of interest.

References


